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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/470,618	12/22/99	COUTO L	AVIGEN-04082

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EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	7

DATE MAILED: 07/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/470,618	Couto et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-40 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-8, 10-15, 17-21, 23-28, and 30-39, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-16, 18-20, and 31-41 of co-pending Application No. 09/364,862. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims are drawn to a method of treating hemophilia in a human, comprising providing at least one recombinant adeno-associated virion comprising nucleotide sequences encoding Factor VIII, and administering said at least one recombinant AAV into said human under conditions such that said Factor VIII nucleotide sequences are expressed at a level which provides a therapeutically effective amount in said human; and wherein Factor VIII nucleotide sequences are expressed in the liver of said human.

Similarly, the claims in the co-pending Application No. 09/364,862 are drawn to a method of treating hemophilia in a human comprising providing a recombinant AAV comprising a nucleotide sequence encoding Factor VIII of human origin operably linked to expression control elements and administering said recombinant AAV into said human under conditions which result in long-term expression of Factor VIII protein at a level which provides a therapeutic effect in said human; and wherein said Factor VIII protein is expressed in the liver of said human.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions provide essentially the same method of treating hemophilia in a human by the administration of nucleotide sequences encoding human Factor VIII, in the instant application and any Factor VIII from any origin. The claims overlap in scope since each embrace using Factor VIII from human origin. The difference between the claims of the instant invention and the co-pending application is the scope of the Factor VIII gene used.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-40 are rejected under 35 U.S.C. 112 first paragraph, because the specification while being enabling for a method of treating hemophilia in a human by providing at least one recombinant adeno-associated virion(rAAV) comprising nucleotide sequences encoding Factor VIII of human origin, does not reasonably provide enablement for a method of treating hemophilia in a human by providing at least one rAAV comprising nucleotide sequence encoding Factor VIII of any origin or source, other than humans, as claimed in the instant invention. The specification does not enable one skilled in the art to which it pertains or to which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to a method of treating hemophilia in a human by providing at least one rAAV comprising a nucleotide sequence encoding Factor VIII and administering said at least one rAAV into said human under conditions such that said Factor VIII nucleotide sequences are expressed at a level which provides a therapeutically effective amount in said human. The claims are also drawn to a method of treating a subject suffering from a blood clotting disorder, by administering a first rAAV comprising a nucleotide sequence encoding the light chain of Factor VIII, and a second rAAV comprising a nucleotide sequence encoding the heavy chain of Factor VIII, such that Factor VIII heavy and light chain nucleotide sequences are expressed at a level which provides a therapeutic effect in said subject. The claims are further drawn to a method of treating hemophilia in a mammal by administering a rAAV comprising a nucleic acid encoding Factor VIII operably linked to an expression control element, which when expressed would have a therapeutic effect on said mammal. Finally the claims are drawn to a

method of treating hemophilia A in a mammal by administering a rAAV comprising a nucleic acid encoding Factor VIII lacking a portion of the B-domain region wherein said nucleic acid is operably linked to an expression control element, which when expressed would have a therapeutic effect on said mammal.

2. The *in vitro* and *in vivo* examples in the specification shows that applicant was successful in obtaining human Factor VIII expression in therapeutically effective amounts, both *in vitro* and *in vivo*. The *in vivo* results demonstrate that applicant was successful in obtaining and maintaining physiological levels of Factor VIII in mice models for more than 11 months.

3. It is not readily apparent that one skilled in the art given applicant's disclosure alone, would be able to practice the inventions over the scope as claimed. On page 5 of the specification, applicant states that many different forms of recombinant Factor VIII have been made and tested both *in vitro* and *in vivo* using a variety of different control and regulatory sequences, and that any DNA sequence coding for biologically active Factor VIII can be expressed using the AAV vectors and methods of the present invention. In the instant situation, the claims embrace any Factor VIII sequence from any origin for use with the recited rAAV. The specification gives specifics only for human Factor VIII. It remains unclear that the state of the art regarding Factor VIII at the time of the invention was such that one skilled in the art would have been able to routinely isolate the heavy and light chains of any Factor VIII from any animal with the specified domains, or utilize any form of recombinant Factor VIII from any source or origin for the treatment of hemophilia in a human, as broadly claimed. Such is considered to

require undue experimentation in view of the lack of guidance provided in the specification as filed.

In the absence of specific guidance which is lacking in the specification as filed, and given the state of the art at the time of filing, it would require undue experimentation for one skilled in the art to practice the claimed methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require the identification of Factor VIII from any and all sources, the isolation of heavy and light chains from Factor VIII and the characterization of delineated domains. One would have had to screen and characterize innumerable Factor VIII proteins for the heavy and light chains, as well as the domains with the intended functionality. The artisan would be left to "trial and error" experimentation to choose appropriate sources of Factor VIII from a variety of possible sources, followed by the isolation of the recited domains, the heavy and light chains.

It would also require undue experimentation to determine which Factor VIII, from which source would necessitate the deletion of the B-domain such that it would be accommodated by rAAV. One must also determine how to achieve and maintain detectable levels of Factor VIII in human plasma, utilizing Factor VIII from any and all sources, such that said Factor VIII would not be subjected to *in vivo* proteolysis.

According to Dodds et al, 1997: "experience with Factor VIII gene transfer is more limited as compared with Factor IX, because full length Factor VIII cDNA is too large to be

accommodated in many currently available vectors. In addition, the half-life of human Factor VIII in human plasma is only 10-12 hours, while in murine plasma, it is less than 1 hour, which makes it harder to achieve detectable levels of human Factor VIII in murine model systems. Finally, expressed Factor VIII must gain easy and rapid access to the circulation to bind to von Willie brand factor(vWf), a carrier protein which stabilizes Factor VIII in the plasma thereby protecting Factor VIII from *in vivo* proteolysis(Dodds et al, see page 129, 1st para)".

Hence, the specification while being enabling for the method of treating hemophilia in vivo by utilizing a rAAV encoding human Factor VIII, does not provide enablement for any and all sources of Factor VIII which when encoded, would express Factor VIII in therapeutically effective amounts to treat hemophilia in a human.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

July 14, 2000

JOHN L. LeGUYADER
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